IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	08/913,257
Filed	:	March 8, 1996
Art Unit	:	1621
Patent No.	:	**6,034,267**
Issue Date	:	March 7, 2000
Applicant	:	Gierskcky et al.
Title	:	ESTERS OF 5-AMINOLEVULINIC ACID AS PHOTOSENSITIZING AGENTS IN PHOTOCHEMOTHERAPY

By Mail

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Hatch-Waxman PTE Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: 11/9/07

Signature: Rita Hassan

Request for Reconsideration of

Final Determination of Ineligibility for Patent Term Extension

To the Commissioner for Patents:

This is in response to the Notice of Final Determination of Ineligibility for Patent Term Extension (the "Notice") of the above-referenced United States Patent No. 6,034,267 ("the '267 patent") under 37 C.F.R. § 1.750. The Notice is dated April 11, 2007.

The Notice provides two months to respond and provides that the response period may be extended pursuant to 37 C.F.R. § 1.136. Applicants hereby petition for a five-month extension of time and authorize the Patent and Trademark Office ("PTO") to charge the applicable extension fee, and any additional required fees, to Deposit Account No. 11-0600.

Applicants further traverse and request reconsideration of the Final Determination of Ineligibility under 37 C.F.R. § 1.750. In rejecting Applicants' request for patent term extension, the Commissioner primarily relies on the decision in *Glaxo Operations UK Ltd. v. Quigg,* 706 F. Supp. 1224 (E.D. Va. 1989), *aff'd.*, 94 F.2d 392, 394 (Fed. Cir. 1990). However, an analysis of the Federal Circuit's

decision in *Glaxo* reveals that the Commissioner has misconstrued the court's decision and consequently misapplied the statute to Applicants' request. As explained in further detail below, a proper reading of the relevant case law and statute compels the conclusion that the '267 patent is entitled to patent term extension.

The '267 patent claims, *inter alia*, a method of using methylaminolevulinate hydrochloride in the approved indications. Application for extension is based on the approval of Metvixia™, which contains methylaminolevulinate hydrochloride as the active ingredient. An application for extension of the '267 patent's expiration date from March 8, 2016 to July 27, 2018 (871 days) was originally submitted on September 20, 2004 and resubmitted after the application was lost by the PTO (resubmitted application received by PTO on October 27, 2006).

35 U.S.C. § 156 provides for the extension of a patent term when the patent claims a product that has been approved for commercial marketing and various other conditions are met. *See* 35 U.S.C. § 156. More particularly, the statute requires that "the product has been subject to a regulatory review period before its commercial marketing or use" (35 U.S.C. § 156(a)(4)), and that "the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred" (35 U.S.C. § 156(a)(5)(A)). The statute further defines "product" to mean "[a] drug product," and "drug product" to mean "the active ingredient of...a new drug...including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f).

In the Notice, the Commissioner acknowledges that the active ingredient in Metvixia™ is methylaminolevulinate hydrochloride. Yet, the Notice wrongly concludes that the earlier-approved Levulan®, which contains aminolevulinic acid hydrochloride as active ingredient – rather than methylaminolevulinate hydrochloride– is the first permitted commercial marketing or use of the "product" under 35 U.S.C. § 156(a). In doing so, the Commissioner interpreted *Glaxo* to require consideration of whether or not the active ingredient in Applicants' product, Metvixia™, is an ester of the active ingredient in Levulan®.

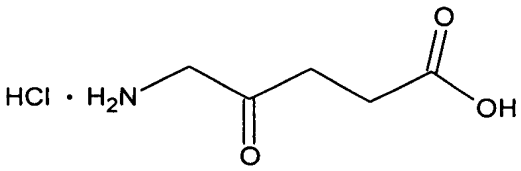
However, as explained below, the Commissioner has misapplied *Glaxo*. As framed by the Federal Circuit's decision, the proper inquiry is simply, based on the plain language of the statute, whether or not the active ingredient in Levulan®, namely, aminolevulinic acid hydrochloride, is an ester (or the same as or a salt) of the active ingredient of Metvixia™. It is not, and in accordance with *Glaxo*, Applicants' request for patent term extension should be granted.

More particularly, in *Glaxo*, the applicant sought a patent term extension based on the approval of the ester cefuroxime axetil. The Commissioner originally rejected the request, based on the prior approval of certain cefuroxime acid salts. In doing so, the Commissioner theorized that the statutory term "product" encompassed new active "moieties," which "would encompass *all* acid, salt, or ester forms of a single therapeutically active substance even if the drug before being administered contained only other substances." *Glaxo*, 894 F.2d at 394. The Commissioner further asserted that the applicant's ester was metabolized (after oral administration and digestion) to form the same therapeutically active substance contained in the previously approved salts.

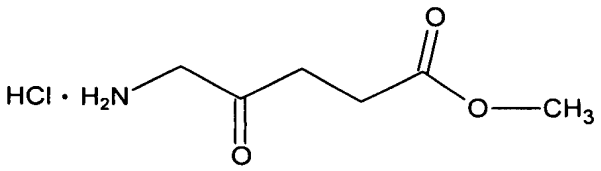
On appeal, the lower court and the Federal Circuit both rejected the Commissioner's position that the term "product" could be construed to mean "active moiety." Rather, both courts determined that the statutory term "product," properly construed according to the "plain meaning" statute, refers only to the "active ingredient" of the applicant's approved product, or a "salt or ester of the active ingredient." *See id.* at 394, 398, 399-400. The courts therefore concluded that the applicant's ester had not been previously approved for commercial marketing or use, even though the acid salts had been approved first, because the acid salts were not the same as, or salts or esters of, the approved ester. *See id.* at 394, 399-400. The patent claiming the ester therefore qualified for extension in part because it claimed an approved "product" that had not previously been approved for commercial marketing or use.

Similarly, here, the active ingredient of Metvixia™ is the hydrochloride salt of the ester methylaminolevulinate, whereas the active ingredient of Levulan® is the hydrochloride salt of the acid aminolevulinic acid. Aminolevulinic acid

hydrochloride is not the same as, or a salt or ester of, methylaminolevulinate hydrochloride. The product methylaminolevulinate hydrochloride therefore has not been previously approved because aminolevulinic acid hydrochloride does not "[fall] within the definition" of "product" as that term is properly construed. *See Glaxo*, 894 F.2d at 394. It therefore follows that Metvixia™ is not precluded from patent term extension eligibility by the previous approval of aminolevulinic acid hydrochloride.[1]



ALA hydrochloride



methyl aminolevulinate hydrochloride

We note in passing that, in addition to *Glaxo*, the PTO cites *Fisons v. Quigg*, 8 U.S.P.Q.2d (BNA) 1491, 1988 U.S. Dist. LEXIS 10935 (D.D.C. 1988), *aff'd*, 10 U.S.P.Q.2D (BNA) 1869, 876 F.2d 99 (Fed. Cir. 1989), in support of its conclusion of ineligibility. With due respect, Applicants note that *Fisons* is not on point. In *Fisons*, applicants obtained approval for a formulation that contained an active ingredient (cromolyn sodium), and subsequently applied for patent term extensions based on the subsequent approval of different formulations containing, and a different indication using, the identical active ingredient (cromolyn sodium). The court held that no extension based on approval of the later approved formulations or indications could be obtained because they were not the first permitted commercial marketing or use of the product, meaning the active ingredient. *See Fisons*, 1988 U.S. Dist. LEXIS at *1-*8, *13-*16, and *32-*35.

---

[1] The same result should be reached regardless of whether or not methyl aminolevulinate is metabolized *in vivo* to yield aminolevulinic acid or another metabolite. As emphasized by the Federal Circuit in an analogous case, for the purpose of patent term extension the "active ingredient" must be present in the drug product when administered as opposed to any potential metabolite. *See Hoechst-Roussel Pharms. Inc. v. Lehman*, 109 F.3d 756 (1997), where the court stated as follows:

> "The statute defines 'product' to include a 'drug product,' 35 U.S.C. § 156(f)(1), which, in turn, is defined as the active ingredient of a drug that receives FDA approval, 35 U.S.C. § 156(f)(2)(A). For purposes of patent term extension, this active ingredient must be present in the drug product when administered. Although the term 'product' in the statute includes any salt or ester of the active ingredient of a drug that receives FDA approval, 1-hydroxy-tacrine [a tacrine hydrochloride metabolite] is neither a salt nor an ester of tacrine hydrochloride.

Hoechst, 109 F.3d at 757 and 759 n.3 (internal citations omitted).

In contrast, here, Applicants applied for an extension based on approval of a product that contains methylaminolevulinate hydrochloride, which is a different active ingredient from that in the previously approved Levulan® (aminolevulinic acid hydrochloride). Unlike in *Fisons*, Applicants here do not rely on the fact that Metvixia™ is a different formulation or indicated for different uses than Levulan®. Rather, Applicants here rely on the fact that, under the statute, methylaminolevulinate hydrochloride was not approved before, despite the prior approval of Levulan® containing aminolevulinic acid hydrochloride.

Moreover, there are substantial differences between methyl aminolevulinate hydrochloride and ALA hydrochloride, as evidenced by the attached Declaration of Dr. Kristian Berg in Support of Grant of Patent Term Extension with Respect to U.S. Patent No. 6,034,267 and accompanying exhibits. These include substantial differences in selectivity of uptake by target lesions, penetration of target lesions, (unwanted) systemic distribution, pain resulting from use in PDT, and mechanisms of cell uptake. Accordingly, methyl aminolevulinate hydrochloride should not be considered the same "product" as aminolevulinic acid hydrochloride (regardless of how "product" is construed).[2]

[2] In other words, aminolevulinic hydrochloride should not be considered to contain the same 'active ingredient" (or salt or ester) or "active moeity" as methyl aminolevulinate hydrochloride, in view of the substantial differences in properties observed.

For the reasons set forth above, Applicants maintain that Levulan® and Metvixia™ should not be deemed the same "product" under 35 U.S.C. § 156(a). In light of these legal and factual distinctions, Applicants request that the determination of ineligibility be rescinded and that the '267 patent be found eligible for patent term extension under 35 U.S.C. § 156.

Respectfully submitted,

Dated: November 9, 2007

By: Deborah A. Somerville
Reg. No. 31995

KENYON & KENYON LLP
One Broadway
New York, New York 10004
(212) 425-7200
CUSTOMER NO. **26646**